Viral Hemorrhagic Fevers

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Viral Hemorrhagic Fevers

- Fever, myalgia, headache, prostration
- Hemorrhage
- Capillary leak
- · Hypotension, shock, death

Hemorrhagic Fever

An acute febrile illness characterized by malaise, myalgia, and prostration dominated by generalized abnormalities of vascular permeability, and regulation. Bleeding manifestations often occur, particularly in severe cases; they are usually diffuse and reflect widespread vascular damage rather than life-threatening volume loss.

Hemorrhagic Fever Viruses: Taxonomy

- Four families of lipid-enveloped viruses with single-stranded RNA genomes
 - Arenaviruses
 - " Bunyaviruses
 - " Filoviruses
 - " Flaviviruses

Hemorrhagic Fever Virus Families

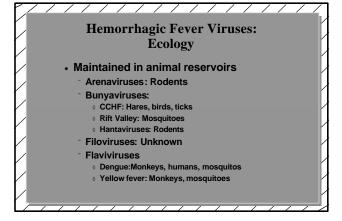
Arenaviridae

- New World Complex
 - Junin Virus Argentine HF
 - Machupo Virus Bolivian HF
 - Venezuelan HF Guanarito Virus
 - "Sabia Virus Brazilian HF
- Old World Complex
 - Lassa Fever Lassa Virus

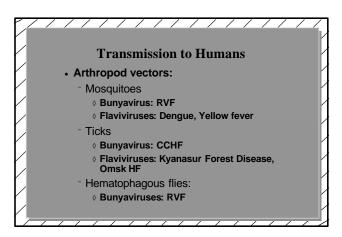
Hemorrhagic Fever Virus Families Bunyaviridae

- Phlebovirus Genus
 - RVF Virus Rift Valley Fever
- Nairovirus Genus
 - Crimean-Congo HF CCHF Virus
- · Hantavirus Genus
 - - Korean or Epidemic HF Hantaan
 - E. Europe Dobrava-Belgrade
 - Nephropathia Epidemica Puumula Virus
 - Rat-borne

Hemorrhagic Fever Virus Families Filoviridae Ebola Virus Ebola HF Marburg Virus Marburg HF Flaviviridae Mosquito-Borne: YF Virus Yellow Fever Dengue Viruses Dengue HF Tick-Borne: Kyasanur Forest Disease KFD Virus Omsk HF **OHF Virus**



Transmission to Humans • Aerosols • Desiccated rodent excreta: Arenaviruses, hantaviruses • Generated by field mice caught in agricultural machinery: New World arenaviruses • Generated during slaughter of infected livestock: CCHF, RVF • Contaminated food/water • Arenavirus (Lassa)



Transmission to Humans: BW Implications • With exception of dengue, all VHF agents transmitted by aerosol in laboratory (animal models) • Stabilization in aerosols

Are Viral Hemorrhagic Fevers
Important Health Problems?

Global interest in VHFs:Most of world population at risk

Argentine HF

100-1000's of cases disruptive to agriculture

Lassa fever

up to 20% of febrile admissions in some W.
Africa hospitals

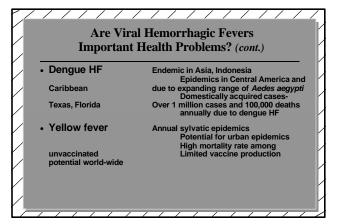
Rift Valley fever

broad distribution in Africa; epidemics in 1977,1993-4, 1998

Congo-Crimean HF

broad geographic distribution epidemics and nosocomial outbreaks

Are Viral Hemorrhagic Fevers Important Health Problems? (cont.) • HFRS Annual epidemics in Asia and elsewhere Broad geographic distribution Up to 200,000 cases annually, with half occurring in China Cases among US troops in Korea and Bosnia Seoul virus infects urban rats in USA 3 cases HFRS due to Seoul virus identified in Baltimore



Military Relevance: Endemic/Epidemic VHF

- · International Deployments
- Risk of Importation/Exportation of Disease
- Impact on Training and Mobilization
- Impact on Medical Readiness

Military Relevance: Biological Warfare Threats

- Pro:
 - Highly infectious by aerosol
 - ♦ Stabilizers to enhance viability
 - High morbidity/mortality
 - Replicate well in cell culture
- Con:
 - " Lack of vaccine/Rx to protect user

Viral Pathogenesis

- Complex, incompletely understood, varies with specific viruses
- · Activation of complement/cytokine cascades
- Activation of coagulation cascades
- · Role of organ system failures
 - Yellow Fever: Hepatic failure, deficiency of Vitamin K dependent clotting factors
 - * HFRS: Uremia, platelet dysfunction
- · Key event: Damage to vascular endothelium

Typical VHF Patient

- History
 - Foreign travel to endemic or epidemic area
 - Rural environs (except dengue, urban YF)
 - " Nosocomial exposure
 - Contact with arthropod or rodent reservoir
 - Domestic animal blood exposure (CCHF, RVF)
- Incubation
 - Typical 5-10 days
 - Range 2-16 days (except Hantavirus: 9-35 days)

Typical VHF Patient Symptoms Fever, headache, malaise, dizziness Myalgias Nausea/vomiting Initial Signs Flushing, conjunctival injection Periorbital edema Petechiae Positive tourniquet test

VHF Evolution Prostration Pharyngeal, chest or abdominal pain Mucous membrane bleeding, ecchymosis Shock Usually improving or moribund within a week (except HFRS, arenaviruses) Bleeding, CNS involvement, marked elevation SGOT portend poor prognosis

VHF Sequelae Prolonged Convalescence Hair Loss, Furrowed Nails Deafness (Lassa, EBO) Retinitis (RVF, KFD) Uveitis (RVF, MBG) Encephalitis (AHF, BHF, RVF, KFD, OHF) Pericarditis (Lassa) Renal insufficiency (HFRS)

Hypotension

VHF Clinical Lab Leukopenia is suggestive, but WBC may be normal, elevated, or leukemoid Thrombocytopenia is typical, but sometimes mild or absent Hematocrit normal or increased early AST (SGOT) typically elevated; prognostic value BUN/Cr related to circulatory status (except in HFRS)

Mortality agent dependent (<10-90%)

VHF Clinical Lab (cont.) Bilirubin, amylase may be elevated Prothrombin/APTT usually prolonged FSP normal or modestly elevated Fibrinogen elevated, normal, or decreased Proteinuria usual

VHF: Differential Diagnosis • Bacterial • typhoid fever, meningoccemia, rickettsioses, leptospirosis • Protozoal • falciparum malaria • Other • vasculitis, TTP, HUS, heat stroke

Diagnosis of Zoonotic Viruses

- · Epidemiology critical
- · Clinical impressions valuable but often ambiguous
- Exclude life-threatening items in DDX:
 - Bacterial sepsis:blood cultures
 - Malaria: thick and thin blood smears (Giemsa stain)
- · Laboratory Confirmation:
- · Rapid ELISA techniques most easily employed
 - viral antigen detection sensitive to ~104 log PFU/ml
 - " IgM antibody capture
- Serology on paired sera may be definitive or highly suggestive

Laboratory Confirmation (Cont'd)

- Nucleic acid hybridization & immunohistochemistry (IHC) of formalin-fixed tissues; Electron microscopy
 - can provide definitive evidence
- · Virus isolation from acute blood or necropsy best
- · Polymerase chain reaction (PCR)
 - increasingly important tool; undergoing further development

Processing Clinical Specimens

- · isolation of virus (Biosafety Level 4)
 - whole blood (w/ anticoagulant)
 - " urine, throat swab or wash
 - $_{\circ}\,$ in sealed plastic tube w/10% FBS or 1%HSA final conc.
 - label each specimen swab exterior of each container with disinfectant
 - double-bag, swab exterior with disinfectant before removal from patient's room

VHF Management: Cardiovascular

- Hemodynamic resuscitation & monitoring
 - invasive (S-G catheter) as warranted and feasible

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- Careful fluid management
 - use of colloid
 - hemodialysis or hemofiltration as needed
 - ♦ esp. HFRS patients
- · Vasopressors and cardiotonic drugs
- Cautious sedation and analgesia

VHF Management Hematologic

- DIC may be important in some VHFs (RVF, CCHF, Filoviruses)
- Coagulation studies and clinical judgement as guide
 - replacement of clotting factors
 - platelet transfusions
- No antiplatelet drugs or IM injections

VHF Management Anti-viral Therapy

- Ribavirin
 - " Arenaviridae (Lassa, AHF, BHF)
 - " Bunyaviridae (HFRS, RVF, CCHF)
- Immune (convalescent) plasma
 - * Arenaviridae (AHF, BHF, ?Lassa)
 - Passive immunoprophylaxis post-exposure?

Lassa Fever & CCHF Management Ribavirin

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- Treatment
 - 30 mg/kg IV single loading dose
 - 16 mg/kg IV q 6 hr for 4 days
 - 8 mg/kg IV q 8hr for 6 days
- Prophylaxis
 - 500 mg PO q 6 hr for 7 days

Note: Parenteral and oral ribavirin are investigati available through human use protocols only

McCormick JB et. al. N Eng J Med 314(1):20-26, 1986 Jahrling PB et al. J Infect Dis 141:580-589, 1980.

HFRS Therapy Ribavirin

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- fever of ≤ 6 days
- intravenous ribavirin treatment regimen:
 - 33 mg/kg (2.0 gm/60kg) single loading
 - 16 mg/kg (1.0 gm/60kg) q 6h for 4
 - 8 mg/kg (0.5 gm/60kg) q 8h for 3 days

Huggins et. al. *J Infect Dis* 164:1119-27, 1991. Note: parenteral ribavirin is investigational and available through human use protocol only

VHF Management Other

- · R/O or treat empirically for malaria, typhoid fever, rickettsioses, etc.
- vigilance against secondary bacterial infections
 - nosocomial pneumonia, UTI, bacteremia

ONLY INTENSIVE CARE WILL SALVAGE THE SICKEST PATIENTS

Infection Control

(Arenavirus, Filovirus,

- Single room w/ adjoining anteroom as only entrance
- Handwashing facility with decontamination solution
 - 0.5% sodium hypochlorite, 2% glutaraldehyde, phenolic detergent, soap
 - Changing area/protective equipment
- · Negative air pressure; air not recirculated
 - Prominent hemorrhage, cough, vomiting, diarrhea
 - Consider negative air flow room, if available, in absense of these sxs/sxs to avoid having to transfer pt later

CDC. Update: Management of patients with suspected viral hemorrhagic fever. *MMWR* 44 (No. 25):475–479, June 30, 1995.
CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Infection Control

(Arenavirus, Filovirus, CCHF) (Cont'd)

- Strict barrier precautions
 - gloves, gown, mask, shoe covers, protective eyewear/faceshield
- · HEPA-filtered mask or respirator
 - Prominent hemorrhage, cough, vomiting, diarrhea

CDC. Update: Management of patients with suspected viral hemorrhagic fever. MMWR 44 (No. 25):475-479, June 30, 1995.

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Infection Control Arenavirus, Filovirus, CCHF

- · Chemical toilet
- (cont.)
- · All body fluids disinfected
- · Disposable equipment & sharps into rigid containers containing disinfectant -> autoclaved or incinerated
- Double-bag refuse
 - outside bag disinfected then autoclaved or incinerated

CDC. Update: Management of patients with suspected viral hemorrhagic fever. MMWR 44 (No. 25):475–479, June 30, 1995. CDC. Management of patients with suspected viral hemorrhagic fever. MMWR 37 (No. S-3):1-15, February 26, 1988.

VHF Management Protection of Medical Personnel

- Patient care limited to minimal # of caregivers
 - reliable and competent-minimize exposure risk
- Education
 - barrier nursing practices, exercise of due care
 - " consult AIT, USAMRIID

DO NOT PANIC

High Level Containment

Disadvantages

- · systems hinder patient care
- · increase possibility of parenteral exposure
- personnel must be trained to safely and effectively function
- · require similar BL-4 laboratory support
- expensive
- 1º & 2º medical care personnel must deal w/ suspected VHF patient before such specialized help is available

Clinical Laboratory Procedures

- · Strict barrier precautions
 - gloves, gown, mask, shoe covers, protective eye/faceshield
 - consider respirator with HEPA filter
 - handle specimens in biosafety cabinet when possible
- · Spills/splashes
 - immediately cover with disinfectant, allow to soak for 30'
 - wipe with absorbent towel soaked in disinfectant
- Waste disposal
- same as for patient isolation practices

CDC. Management of patients with suspected viral hemorrhagic fever. MMWR37 (No. S-3):1-15, February 26, 1988.

ExposuresFirst Aid

- · Wash/irrigate wound/site immediately
 - within 5 minutes of exposure
- · Mucous membrane (eye, mouth, nose)
 - continuous irrigation with rapidly flowing water or sterile saline for ≥ 15 minutes
- Skin
 - scrub for at least 15' minutes while copiously soaking the wound with soap or detergent solution
 - fresh Dakin's solution (0.5% hypochlorite): dilute 1 part standard laundry bleach (5% hypochlorite) with 9 parts tap water

Exposures: Surveillance

- Casual contacts
 - * remote contact with index patient (e.g., same airplane)
- no known risk
- Close contacts
 - household, physical, nursing care, handling lab specimen
 - " record temp b.i.d. for 3 weeks post-exposure
 - post-exposure prophylaxis measures warranted if develop fever (T≥101F) or other systemic symptoms within 3 weeks post-exposure

CDC. Management of patients with suspected viral hemorrhagic fever. *MMWR* 37 (No. S-3):1-15, February 26, 1988.

Post-Exposure Prophylaxis

- · High-risk contacts
 - " mucous membrane (e.g., kissing, sexual intercourse); needlestick or other penetrating injury involving exposure to patient's secretions, excretions, blood, tissues, or other body fluids
 - post-exposure prophylaxis measures warranted if available

VHF Vaccines

- YELLOW FEVER
 - ⁻ licensed 17D vaccine safe and efficacious

" cannot be used in persons with egg allergy

• ARGENTINE HEMORRHAGIC FEVER

- live, attenuated
- safe and efficacious; used in 150,000
- protects monkeys against Bolivian HF

VHF Vaccines

• RIFT VALLEY FEVER

- formalin-inactivated
 - safe but requires 3 shots, intermittent booster
 - ◊ limited supply
- ive, attenuated MP-12
 - ◊ Phase II testing
- · HFRS (HANTAAN)
 - vaccinia vectored recombinant vaccine

Aeromedical Isolation Team

High-level protection against small-particle aerosol infection

- * Plastic isolator for transport stretcher
- negative pressure with HEPA exhaust
- Positive pressure suits for medical personnel

Medical consultation

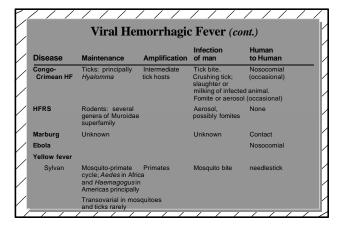
- " contact USAMRIID and ask for MOD on call
 - ♦ DSN 343-2257, (301) 619-2257
- Transport arrangements

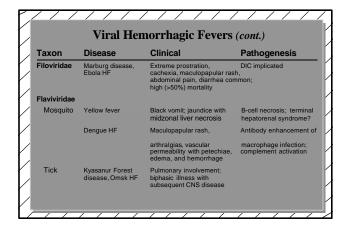
 - o can transport 1-2 patients

Disease	Geography	Source of Human Infection ^a	Incubation (days)
Lassa	Africa	Rodent (Nosocomial)	5-16
AHF/BHF	South America	Rodent	7-14
RVF	Africa	Mosquito (Slaughter)	2-5
CCHF	Europe, Asia, Africa	Tick (Slaughter of domestic animal)	3-12
HFRS	possibly world-wide	Rodent	9-35
Marburg/Ebo	la Africa	Unknown (Nosocomial)	3-16
Yellow Fever	Tropical Africa, South America	Mosquito	3-15
Dengue HF	Asia, Americas, Africa	Mosquito	3-15
KFD/OMSK	Mysore, India/ Russia	Tick (Muskrat- contaminated water)	3-8

Viral Hemorrhagic Fevers				
Taxon	Disease	Clinical	Pathogenesis	
Arenaviridae	Lassa fever	Hemorrhage & neurologic involvement seen in severe cases; deafness; pericarditis may occur during recovery	High AST and viremia predict fatal outcome	
	Argentine & Bolivian HF	Prominent neurologic manifestations; petechiae and hemorrhage common	Bone marrow and CNS infection	
Bunyaviridae	•			
Phlebovirus	Rift Valley fever	retinitis; hemorrhage and hepatitis with icterus occur infrequently	DIC in monkey model	
Nairovirus	Crimean- Congo HF	copious hemorrhage & extens ecchymoses may dominate clinical picture more prominen than with other HF		
Hantavirus	Hemorrhagic fever with renal syndrome	Renal involvement prominent intrinsic disease feature; long incubation period	Tubular lesion. Onset of disease correlates with immune response	

Disease	Maintenance	Amplification	Infection of man	Human to Human		
Lassa	Rodent: Mastomys natalensis		Aerosol, fomites	Contact Nosocomial (occasional)		
Argentine HF	Rodent: Calomys musculinus	Other rodents?	Aerosol, fomites	Venereal (occasiona Nosocomial (rare)		
Bolivian HF	Rodent: Calomys	callosus	Aerosol, fomites	Venereal (suspected Nosocomial (rare)		
Rift Valley fever	Mosquito: flood water Aedes	Sheep & cattle with other mosquitoes	Mosquito bite (biological transmission, interrupted feeding	needlestick		
			Aerosol or fomites from slaughter of domestic animals			





Viruses	Disease	In vitro neutralization by convalescent sera	In vitro Interferon Sensitivity	Ribavirin
		convalescent sera	Sensitivity	Kibavirii
<u>Arenaviridae</u>	Lassa fever Argentine & Boliviar	+ n HF ++	low low	yes yes
<u>Bunyaviridae</u>				
Phlebovirus	Rift Valley fever	+++	yes	yes
Nairovirus	Congo-Crimean HF		yes	yes
Hantavirus	HFRS, HPS	+++	yes	yes
<u>Filoviridae</u>	Marburg disease, Ebola HF	0	low	no
<u>Flaviviridae</u>				
Mosquito borne	Yellow fever	+++	yes	low
	Dengue HF	+++	yes	low
Tick borne	Kyasanur Forest disease, Omsk HF	+++	yes	low

Argentine, Bolivian, and Venezuelan Hemorrhagic Fevers

- · rodent-borne (aerosol) in South America
 - " nosocomial transmission rare
- petechiae & other hemorrhages neurologic manifestations w/ normal CSF
- · incubation period 7-14 days
- shock, pulmonary edema, GI hemorrhage, CNS dz (tremors, dysarthria, seizures)
- lab: low wbc, plt, and complement; proteinuria, prerenal
- Dx: Ag detection and IgM capture ELISA virus isolation (serum, buffy coat, semen)

Lassa Fever

- · rodent-borne in West Africa
 - " nosocomial: exposure to body fluids
- pharyngitis with exudate, hypotension, cough, abd pain, edema and effusions, lymphadenopathy
 - hemorrhage not common except in severe cases
 - deafness, pericardial friction rub during recovery
- incubation period 5-16 days
- elevated AST, CPK, and amylase; protenuria; mildly low or normal wbc and plt
- Dx: Ag detection and IgM capture ELISA virus isolation from serum, urine, throat

Congo-Crimean Hemorrhagic Fever

- tick-borne in Africa, Asia, E. Europe, Middle East
 - nosocomial via body fluid exposure (?aerosol)
- extensive hemorrhage and ecchymoses, hypotension, hepatomegaly, abdominal pain, jaundice, toxicity
- · incubation period 3-12 days
- Low plt & fibrinogen, elevated PT/PTT & FSP, lymphopenia, elevated LFT's and bili
- Dx : Ag detection and IgM capture ELISA virus isolation (serum)

Rift Valley Fever

- · mosquito-borne in sub-Saharan Africa
 - nosocomial infection not reported but aerosol transmission possible
- · fever, headache, myalgias, retinitis
 - infrequently complicated by hemorrhage, severe hepatitis with jaundice, and/or encephalitis
- · incubation period 2-5 days
- low wbc and plt, transaminitis with elevated bili and alk phos, prolonged PT/PTT
- Dx : Ag detection and IgM capture ELISA virus isolation (serum)

Hemorrhagic Fever with Renal Syndrome

- · rodent-borne (aerosol)
 - HFRS: Asia (Hantaan, Seoul), Europe (Hantaan, Dobrava), USA (Seoul)
 - nephropathia epidemica in Europe (Puumala)
 - May complicate HPS due to Bayou, Black Creek Canal, and South American hantaviruses
- · fever, shock, hemorrhage, renal failure
- incubation period 9-35 days
- · low plt, renal azotemia
- Dx : IgM capture ELISA

Ebola and Marburg

- · unknown reservoir in Central and East Africa
 - nosocomial: transmission usu. via exposure to body fluids, but possible by fomite or droplet
- severe prostration with delirium, maculopapular rash, DIC
 - abdominal pain, petechiae, GI hemorrhage, hepatitis, edema, prerenal azotemia, shock
- · incubation period 3-16 days
- low wbc, plt; positive FSP; transaminitis; proteinuria, azotemia
- Dx: virus isolation from serum, urine, semen, throat or rectal swab

Yellow Fever

- mosquito-borne in tropical Americas and sub-Saharan Africa
- jaundice, midzonal liver necrosis, black vomit, relative bradycardia
- · incubation period 3-15 days
- low wbc and plt, proteinuria, elevated SGOT, prolonged PT/PTT
- Dx : IgM capture ELISA virus isolation (serum)

Dengue Hemorrhagic Fever

- · mosquito-borne in tropical Americas, Africa, Asia
- maculopapular rash sparing palms and soles, arthralgias, capillary friability
 - positive tourniquet test, petechiae and mucosal hemorrhage, shock
- · incubation period 3-15 days
- low plt and fibrinogen, lymphocytosis, hemoconcentration, depressed C3 and C4
- Dx : IgM capture ELISA virus isolation (serum, buffy coat)

Pathogenesis: Dengue Hemorrhagic Fever

- Four different serotypes of Dengue virus
- Initial infection: Neutralizing Ab vs. intial strain
- Re-infection due to different serotype:
 Non-neutralizing Ab
 - * Immune complexes c live virus
- Enhanced uptake by monocytes
- Infection/lysis of monocytes-release of cytokines, anticoagulants, procoagulants
- Implications re vaccine development

Kyasanur Forest Disease Omsk Hemorrhagic Fever

- tick-borne in India (KFD) and Siberia (Omsk)
 - " nosocomial transmission not reported
- systemic toxicity, pulmonary infiltrates biphasic course with later CNS involvement
 - becomes afebrile, then develops neurologic disease
- incubation period 3-8 days
- low wbc and plt
- Dx: IgM capture ELISA